AMENDMENT TO THE CLAIMS

1. (Previously Presented) A method of biomarker discovery, said method comprising the steps of:

providing a complex analyte as a candidate biomarker source, said complex analyte being depleted of abundant proteins;

providing a control sample for said complex analyte;

injecting a model animal with an aliquot of said abundant protein-depleted complex analyte as an immunogen so as to generate, from individual hybridoma cell lines, a population of monoclonal antibodies directed against antigens in said complex analyte;

screening said population of monoclonal antibodies directed against antigens in said complex analyte against another aliquot of said complex analyte;

screening said population of monoclonal antibodies directed against antigens in said complex analyte against an aliquot of said control sample; and

selecting at least one monoclonal antibody that exhibits a statistically significant difference in binding to an antigen in said complex analyte compared to an antigen in said control sample, whereby the antigen(s) selectively bound by said at least one selected monoclonal antibody are said biomarker(s).

2. (Original) The method of claim 1, wherein, in said selecting step, said one or more monoclonal antibodies exhibits an increase in binding to an antigen in said complex analyte compared to an antigen in said control sample.

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3. (Withdrawn) The method of claim 1, wherein, in said selecting step, said one or more monoclonal antibodies exhibits a decrease in binding to an antigen in said complex analyte compared to an antigen in said control sample.

4. (Withdrawn) The method of claim 1, wherein said complex analyte is diluted before use as an immunogen.

5. (Previously Presented) The method of claim 1, wherein said complex analyte is depleted of abundant proteins by fractionation before use as an immunogen.

6. (Original) The method of claim 1, wherein said complex analyte is a clinical sample.

7. (Original) The method of claim 6, wherein said complex analyte is a human bodily fluid.

8. (Withdrawn) The method of claim 7, wherein said complex analyte is human blood.

9. (Withdrawn) The method of claim 8, wherein said complex analyte is human plasma.

10. (Withdrawn) The method of claim 8, wherein said complex analyte is human serum.

11. (Withdrawn) The method of claim 7, wherein said complex analyte is human urine.

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12. (Withdrawn) The method of claim 7, wherein said complex analyte is human cerebrospinal fluid.

13. (Withdrawn) The method of claim 6, wherein said complex analyte comprises proteins or peptides.

14. (Withdrawn) The method of claim 13, wherein said complex analyte comprises glycoconjugated proteins or peptides.

15. (Withdrawn) The method of claim 13, wherein said complex analyte comprises a group of disease specific proteins.

16. (Cancelled)

17. (Previously Presented) The method of claim 1, wherein said complex analyte is enriched in a specific class of analyte elements before use as an immunogen.

18. (Original) The method of claim 6, wherein said complex analyte is from an individual patient, wherein said control sample is from one or more healthy individuals and whereby said selecting step identifies a biomarker that distinguishes said patient from said healthy individuals.

19. (Withdrawn) The method of claim 6, wherein said complex analyte is from an asymptomatic individual having increased risk for the disease of interest, wherein said control sample is from one or more healthy individuals and whereby said selecting step

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identifies a biomarker that distinguishes said asymptomatic individual from said healthy individuals.

20. (Withdrawn) The method of claim 6, wherein said complex analyte is from an individual patient who has responded to a treatment, wherein said control sample is from an individual patient who has not responded to said treatment and whereby said selecting step identifies a biomarker that distinguishes an individual patient who will respond to said treatment from an individual patient who will not respond to said treatment.

21. (Original) The method of claim 1, further comprising the step of determining the identity of said biomarker(s).

22. (Previously Presented) The method of claim 1, further comprising the steps of determining the identity of a plurality of said biomarkers.

23. (Previously Presented) A method of biomarker discovery, said method comprising the steps of:

providing a complex analyte as a candidate biomarker source, said complex analyte being depleted of abundant proteins;

providing a control sample for said complex analyte;

injecting a model animal with an aliquot of said abundant protein-depleted complex analyte as an immunogen so as to generate, from individual hybridoma cell lines, a population of monoclonal antibodies directed against antigens in said complex analyte;

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screening said population of monoclonal antibodies directed against antigens in said complex analyte against another aliquot of said complex analyte;

screening said population of monoclonal antibodies directed against antigens in said complex analyte against an aliquot of said control sample;

selecting a plurality of monoclonal antibodies that each exhibits a statistically significant difference in binding to an antigen in said complex analyte compared to an antigen in said control sample, whereby the antigens selectively bound by said plurality of selected monoclonal antibodies are a plurality of said biomarkers; and

determining the identity of said plurality of biomarkers.

24. (Cancelled)

25. (Currently Amended) A method of generating a monoclonal antibody library related to a specific disease or condition, said method comprising the steps of:

providing a complex analyte related to a specific disease or condition as a candidate biomarker source, said complex analyte being depleted of abundant proteins;

providing a control sample for said complex analyte;

injecting a model animal with an aliquot of said abundant protein-depleted complex analyte as an immunogen so as to generate, from individual hybridoma cell lines, a population of monoclonal antibodies directed against antigens in said complex analyte;

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screening said population of monoclonal antibodies directed against antigens in said complex analyte against another aliquot of said complex analyte;

screening said population of monoclonal antibodies directed against antigens in said complex analyte against an aliquot of said control sample; and

selecting a plurality of monoclonal antibodies that each exhibits a significant difference in binding to an antigen in said complex analyte compared to an antigen in said control sample, whereby the ~~antigens selectively bound by said~~ plurality of ~~selected~~ monoclonal antibodies selected as exhibiting a significant difference in binding to an antigen in said complex analyte compared to an antigen in said control sample is ~~are~~ said monoclonal antibody library related to said specific disease or condition.

26. (Previously Presented) A method of biomarker discovery, said method comprising the steps of:

providing a complex analyte as a candidate biomarker source, wherein said complex analyte is related to a biological process of interest;

providing a control sample for said complex analyte;

depleting said complex analyte of one or more abundant proteins;

injecting a model animal with an aliquot of said abundant protein-depleted complex analyte as an immunogen so as to generate, from individual hybridoma cell-lines, a population of monoclonal antibodies directed against antigens in said complex analyte;

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screening said population of monoclonal antibodies directed against antigens in said complex analyte against another aliquot of said complex analyte;

screening said population of monoclonal antibodies directed against antigens in said complex analyte against an aliquot of said control sample;

selecting a plurality of monoclonal antibodies that each exhibits a statistically significant difference in binding to an antigen in said complex analyte compared to an antigen in said control sample, whereby the antigens selectively bound by said plurality of selected monoclonal antibodies are a plurality of said candidate biomarkers;

determining the identity of said plurality of biomarkers; and

identifying individual biomarkers among said plurality of biomarkers that are associated with specific changes in said biological process of interest.

27. (Previously Presented) The method of claim 1, wherein said complex analyte is depleted of abundant proteins that have a numeric complexity of less than 5-10% of the total number and represent at least 50% of the total mass of proteins of the complex analyte.

28. (Previously Presented) The method of claim 6, wherein said complex analyte is from two or more individual patients.

29. (Previously Presented) A method of biomarker discovery, said method comprising the steps of:

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providing a human bodily fluid sample as a candidate biomarker source, said human bodily fluid sample being depleted of abundant proteins that have a numeric complexity of less than 5-10% of the total number and represent at least 50% of the total mass of proteins of said sample;

providing a control sample for said human bodily fluid sample;

injecting a model animal with an aliquot of said abundant protein-depleted sample as an immunogen so as to generate, from individual hybridoma cell lines, a population of monoclonal antibodies directed against antigens in said sample;

screening said population of monoclonal antibodies directed against antigens in said sample against another aliquot of said sample;

screening said population of monoclonal antibodies directed against antigens in said sample against an aliquot of said control sample; and

selecting at least one monoclonal antibody that exhibits a statistically significant difference in binding to an antigen in said sample compared to an antigen in said control sample, whereby the antigen(s) selectively bound by said at least one selected monoclonal antibody are said candidate biomarker(s).

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